STATEMENT OF WORK FOR CORONARY ARTERY DISEASE RISK DEVELOPMENT IN YOUNG ADULTS (CARDIA) STUDY - Ultrasound Reading Center (USRC)

I. INTRODUCTION (Background)

Subclinical atherosclerosis and risk factor development and progression may accelerate in early middle age. Relatively few studies have collected longitudinal data on risk factors that can be linked to subsequent subclinical disease. Identification of risk factors that predict early development and progression of atherosclerosis may provide valuable insights in developing future intervention research and identifying individuals to target for increased translation activities.

The Coronary Artery Risk Development in Young Adults (CARDIA) Study started as a study of the distribution and evolution of risk factors for cardiovascular disease (CVD) during young adulthood in black and white men and women. At Year 20 participants will be in their 40s–an age when the earliest detectable subclinical disease appears to accelerate. CARDIA offers the opportunity to address aspects of the development and progression of subclinical atherosclerosis that cannot be addressed in older cohorts.

The study, which began recruitment in 1985, has completed 6 examinations over 15 years in a cohort of 5,115 men and women aged 18-30 years in four communities. Participants were initially sampled from the total population, selected census tracts or, in the case of one Center, the membership of a large health plan. The original cohort had approximately equal representation by blacks and whites, men and women, those aged 18-24 and 25-30, and those with no more than a high school education and more than a high school education.

The study has four Field Centers and a Coordinating Center, which subcontracts for laboratories and other essential functions. Principal Investigators from each of the Field Centers and the Coordinating Center plus the NHLBI Project Officer form the Study Steering Committee. The chairman of the Steering Committee serves through a subcontract with the Coordinating Center.

The baseline examination (Year 0) was conducted over a 14-month period during 1985-86. The examination consisted of questionnaires on sociodemographic characteristics, health behaviors, and psychological factors; an exercise treadmill test; resting electrocardiography; a diet history assessment; anthropometry; pulmonary function testing; and resting blood pressure. Fasting blood measurements included total cholesterol and its subfractions, insulin, glucose, liver enzymes and other serum chemistry measurements, and hematology.

Five additional examinations have been completed every 2-5 years, including a Year 15 examination completed in 2001. Repeat measurements on traditional risk factors, including plasma lipids, blood pressure, anthropometry, smoking behavior, physical activity, and pulmonary function testing (except Years 7 and 15) have used the same methods at each examination to assess age and secular trends in these factors during young adulthood. In selected

years, additional measurements have been made, including a treadmill exercise test and diet history at baseline and Year 7; cardiovascular reactivity measurements in Year 2; echocardiography and ambulatory blood pressure monitoring (in a subset) at Year 5; skin reflectance and assessment of the experience of discrimination and other psychosocial measures and urine sodium and creatinine in Year 7; echocardiography (in a subset), glucose tolerance testing, and microalbuminuria in Year 10; and a coronary CT scan at Year 15.

Retention of the surviving cohort was 90, 86, 81, 79, and 74 percent at each of the respective follow-up examinations. Cohort members are contacted every six months to obtain information on vital status and current residence. Every other contact includes speaking with the participant to ascertain information on current smoking status, major illness or injury, and hospitalizations.

The objectives for the five year renewal are to:

A. Identify predictors of earlier development and more rapid progression of subclinical atherosclerosis

CARDIA will test which risk factors (established, novel, lifestyle, psychosocial, and socioeconomic) and 20-year patterns of change in them predict development and progression of subclinical disease (measured by coronary CT scan and carotid ultrasound). The impact of long-term vs. short-term exposure to an unfavorable risk profile will be assessed. CARDIA will explore differences in predictors by race, particularly the impact of obesity and its metabolic consequences on widening health disparities. CARDIA will identify whether predictors differ for coronary artery calcification (CAC) and intimal-medial thickness (IMT) and assess the relative contribution of diabetes, renal impairment, and health care access and utilization to subclinical atherosclerosis.

B. Assess racial differences in severity and progression of early subclinical disease to elucidate possible differences in CVD pathogenesis.

CARDIA will address the lower CAC prevalence in blacks than whites despite greater common carotid IMT in blacks observed in older cohorts to assess coronary vs. systemic subclinical atherosclerosis, two distinct pathologies that may reflect racial differences in CVD pathogenesis. CARDIA will test if CAC continues to be more prevalent at Year 20 in whites, if CAC progression differs by race, and if carotid IMT is greater in blacks than whites.

C. Test whether inflammation precedes subclinical disease

CARDIA will address a key question regarding the atherogenic role of inflammation --whether it is causal or instead is reflective of underlying atherosclerosis. CARDIA will test whether C-reactive protein (CRP), other inflammatory markers, and related factors at young ages (18-30 years) are related to subclinical atherosclerosis or if they are associated

only after subclinical disease has reached certain levels. CARDIA also will identify long-term predictors of inflammation (e.g., specific infectious agents vs. cumulative burden), the impact of obesity, particularly visceral adiposity, on the inflammatory process, and how early in adulthood inflammation-associated dysregulation of normal physiology begins.

D. Assess the roles of genetic variation and gene by environment interactions in early development and progression of subclinical disease

CARDIA will address the role of genetic variation and gene by environment interactions in development and progression of subclinical disease and its risk factors. CARDIA will test if genes such as those related to bone mineralization regulation (e.g., matrix Gla, osteopontin), obesity (e.g., leptin receptor), and dyslipidemia (e.g., lipoprotein lipase, APOA1) are associated with CAC and IMT.

Measures to be repeated in the Year 20 exam include CAC, established risk factors, oral glucose tolerance test, diet history, physical activity, lung function, electrocardiogram (ECG), CRP, microalbuminuria, and serum creatinine. About 50 polymorphisms will be genotyped. New measures will include carotid ultrasound to measure IMT and inflammatory and related markers not previously collected in CARDIA.

II. SPECIFIC REQUIREMENTS AND TASKS

Note: Throughout this statement of work, the terms "Contractor" and "Reading Center" are used interchangeably to facilitate description of the tasks to be performed.

Independently, and not as an agent of the Government, the Contractor, in conjunction with the other Field Centers and Coordinating Center, shall provide services, qualified personnel, equipment, facilities, and materials, not otherwise provided by the Government, to perform the following work:

A. General Requirements and Tasks

1. Coordinate, at the direction of the Steering Committee and in collaboration with the Coordinating Center and Field Centers, the development of protocols for carotid artery ultrasound scans at each Field Center, and ultrasound reading and information abstraction at the Reading Center in accordance with the study design.

2. Train, certify, and monitor performance of Field Center sonographers according to the ultrasound scanning protocol. This will include training and certification of initial and new sonographers due to turnover and site visiting the four Field Centers during the first 4-6 weeks of the Year 20 exam and later as needed in support of quality control monitoring of the Coordinating Center. It will also include orientation training to ultrasound scanning methods for professional staff from the Coordinating Center with quality control responsibilities.

3. Train and certify ultrasound readers at the Reading Center according to the reading and information abstraction protocol. This will include initial training, certification, and orientation in the pilot testing phase and training, certification, and orientation of new readers and quality control staff due to turnover. It will also include orientation of professional staff from the Coordinating Center with quality control responsibilities.

4. Conduct a pilot test of the ultrasound protocol, including monitoring and evaluation for quality control, during the protocol development/pilot testing phase, in collaboration with Field Centers and the Coordinating Center.

5. Perform readings and information abstractions of ultrasound scans on approximately 3,530 studies, including studies from the pilot phase, the 12-month examination period (June 1, 2005 to May 31, 2006), and rereads and repeat scans for quality control during the examination.

6. Participate in various other activities including participating in the Steering Committee, Imaging Committee, and other subcommittees as necessary, and participating in data analysis and preparation of reports and manuscripts using the ultrasound data.

III. Specific requirements and tasks:

A. In collaboration with the Imaging Committee, develop and implement protocols for ultrasound scanning.

1. Develop, at the direction of the Steering Committee and in collaboration with the Coordinating Center and Field Centers, a protocol for ultrasound scanning during the Year 20 exam. The protocol will specify the techniques to measure carotid artery wall thickness and atherosclerotic lesion characteristics as well as other potential characteristics of interest in the carotid arteries in an examination not to exceed 30 minutes of participants' time (examination time).

   [Note: For planning purposes, assume that each Field Center will use equipment supplied by the government (LOGIQ 700 Ultrasound Machine, General Electric Medical Systems, Waukesha, WI).]

2. The examination will be sufficient to permit the following quantitative measurements to be made at the Ultrasound Reading Center:

   a. Vessel interfaces; including near and far wall adventitia-periadventitia, media-adventitia, lumen-intima of both common carotid arteries, both carotid bulbs, and both internal carotid arteries.

b. Wall thicknesses; including mean and maximum intimal-medial thickness of near and far walls of both common carotid arteries, both carotid bulbs, and both internal carotid arteries.
c. Minimum residual lumen of the common and internal carotid arteries.
d. Vessel width; including mean and maximum width of the common carotid arteries, carotid bulbs and internal carotid arteries.
e. Doppler frequency shift or velocity at point of maximum disease in the assessment of stenosis.
f. Lesion characteristics such as homogeneity, density, and regularity of surface.

[Note: This list of core measurements is subject to modification either after the Ultrasound Reading Center contract is awarded as a result of protocol development, and/or before award, as a result of recommendations, capabilities and proposed costs of potential contractors.

In response to the RFP, describe the methods to be used for measurement and coding as well as expertise and experience with the proposed methods for each of the measures listed above. Issues of measurement reproducibility and burden to participants and Field Center staff should be included. Recommended deletions from or additions to the above list may be suggested.]

3. Advise Field Centers on identifying the kinds of expertise needed by sonographers to accomplish the proposed measurements. Develop methods for ensuring quality and standardization of ultrasound procedures and readings among Field Centers, including written standard operating procedures (SOPs) to be implemented at Field Centers and sonographer certification procedures. SOP should include: procedures for documentation and records keeping; forms to log incidents reflecting unusual circumstances related to measurements, readings, errors, or any other information that may be of utility in data interpretation; for measurement quality control activities; and for any other relevant activity.

4. Monitor Field Center sonographer performance to ensure uniformity of data collection among field sites throughout the examination period and report results of this monitoring to the Steering Committee.

5. In collaboration with Coordinating Center staff as part of an overall quality assurance program, train and oversee quality control monitoring of scanning from the Field Centers' sonographers in details of the examination, data handling and/or electronic data transfer, and data management. Training may include a meeting at the Reading Center with all Field Center sonographers. Train and certify initially, and retrain and recertify sonographers as needed during the entire study period. Train and certify new sonographers when turnover occurs, as necessary. Assess inter- and intra-individual

variation among sonographers, define limits of acceptability, and work collaboratively with Field Centers to implement necessary corrective actions.

[Note: For proposal purposes assume the Field Center sonographers will have general experience in vascular ultrasound, but need training in specific details of this study. Assume each Field Center will have a physician-ultrasonographer on site to supervise performance of ultrasound studies and to contribute to protocol development, quality assurance, and data analysis.

Specific detailed plans for training, including proposed curriculum and number of studies to be performed by sonographers in training must be included in the proposal.]

6. Prepare web-ready Field Center Manuals of Operations for distribution to interested parties, and provide electronic and/or hard copies of Manuals for distribution to and use by the Field Centers, the Coordinating Center, and the Project Office.

B. In collaboration with the Imaging and Steering Committees, design and implement protocols for reading ultrasound studies.

1. Develop a protocol including written SOPs for ultrasound readings as a means to fully characterize carotid atherosclerosis at Year 20. The readings will measure characteristics listed in section III.A above.

   [Note: The proposal should detail the proposed reading method. The proposal should describe any offline analysis systems to be used, and should provide data on validity and reproducibility of proposed reading methods.]

2. Prepare Web-ready Reading Center Manuals of Operations for distribution to interested parties, and provide electronic and/or hard copies of Manuals for distribution to the Coordinating Center and the Project Office.

3. As part of an overall quality assurance program in collaboration with Coordinating Center staff, train, certify, and monitor for quality control the sonographers in interpretation of studies and reading conventions developed in the final scanning protocol. Train and certify initially, and retrain and recertify sonographers as needed during the entire study period. Train and certify new sonographers when turnover occurs, as necessary.

4. Develop quality control procedures and performance standards to ensure that measurements from each reader conform to protocol requirements. This includes assessment of scan quality, monitoring, and control of inter- and intra-reader variability. In conjunction with the Quality Control committee, define the limits of acceptability and plan for its continual assessment.

C. In collaboration with Coordinating Center staff, design, oversee and evaluate a pilot study of approximately 20 volunteers measured at each Field Center during the protocol development/pilot testing phase, prior to finalization of the Manuals of Operations.

1. Assist in the oversight of performance of measurements in 20 volunteers at each Field Center, according to the protocol developed in III.A above.

    a. Collaborate with the Field Centers and Coordinating Center staff in the collection and analysis of pilot data, including quality control data.
    b. Transmit all data to the Coordinating Center as part of the protocol development/pilot testing phase.

    Note: The draft protocol for ultrasound scanning is to be completed before pilot testing. After the draft protocol has been developed in collaboration with the Imaging Committee and approved by the Steering Committee, staff are to be centrally trained. Pilot testing for the examination is to be conducted after training is complete and OMB clearance has been obtained, and is to consist of performing the examination, according to the draft Manual of Operations, in at least 20 volunteers per Field Center, who are not study participants. The pilot tests are to include transmission of readings of ultrasound data to the Coordinating Center. Final modifications to the protocol and Manual of Operations are to be made based on the pilot test results, at the direction of the Steering Committee.

2. Identify and recommend remedial action prior to the start of the full examination for problems revealed in any aspects of scanning, data handling or reading as a result of the pilot test.

[Note: For the purposes of planning, assume there will be two sonographers at each Field Centers. Assume there will be two readers at the Ultrasound Reading Center, each of whom will initially read half, or 40, of the pilot images. Assume each reader will re–read 100% of these images for the purposes of assessment of intra–reader variability, and will read 100% of the other reader's first reading as a test of inter–reader variability. This will be a total of 240 images processed and read during the pilot test.]

D. Perform readings, information abstractions, and interpretations at a capacity of approximately 65 per week during the examination (approximately 3,410 total studies, including quality control readings) and transfer data to the Coordinating Center.

[Note: It is expected that 3,490 CARDIA participants will undergo the Year 20 exam and that 85% (2,966) will undergo the ultrasound exam during the 12-month exam period, from June 1, 2005 to June 1, 2001. Plan to reread 5% of Year 20 studies by the same and 5% by a second reader. Assessment of intra-reader variability should be performed with each new reader, as appropriate. Also plan to read repeat scans on 5% of participants to assess reproducibility of ultrasound measurements.]

1. Conduct readings in accordance with the protocol approved by the Steering Committee.

   [Note: The proposal should describe the proposed method of performing information abstraction (i.e., "reading" the ultrasound studies), any analysis systems to be used, and should provide data on validity and reproducibility of proposed reading methods.]

2. Perform rereads to assess inter- and intra-individual variation in readers, in accordance with a quality control program developed in collaboration with the Coordinating Center.

3. Transfer ultrasound data to the Coordinating Center within 14 days of receipt of the scans using a format to be determined and mutually agreed upon by the Coordinating Center and Reading Center. The Reading Center must notify the Coordinating Center in advance of, and the Coordinating Center must agree to, any proposed changes in the data transfer format during the exam cycle.

4. Assist the Coordinating Center with edit checks and corrections to the data base.

5. Assist the Coordinating Center in analysis and interpretation of data on accuracy and reliability, including summary of findings and recommendations for any further re-readings or analyses to the Steering Committee, as appropriate.

E. Track the receipt, reading, and storage of ultrasound scans.

   1. Develop and implement methods to assure complete and accurate transfer of scans between the Field Center and the Ultrasound Reading Center, including receiving scans from the Field Centers, verifying that the number of images received matches the number sent according to logs from the Field Centers, and resolving discrepancies with the Field Centers. To ensure that scans were received for each participant who had an ultrasound exam, transmit weekly to the Coordinating Center an electronic list of IDs for participants for whom scans were received that week. Work collaboratively with the Field Centers and Coordinating Center to resolve discrepancies.

2. Develop and implement methods to assure complete and accurate transfer of all data to the Coordinating Center. Data transmission will occur on a regular basis, approximately weekly or as agreed upon in protocol development. The content and format of data transmitted will be developed in collaboration with the Coordinating Center.

3. To ensure that all activities have been performed for each participant's data, maintain an electronic tracking database to include: date scan received from the Field Centers; date read and reader ID; scan quality assessment; reread dates and reader ID if appropriate; date of transmission to Coordinating Center; and location of original and backup copy if appropriate. Share database with Coordinating Center upon request.

4. Develop and implement long-term archiving and storage of ultrasound scans and timely creation of backup copies, including routine transfer of a copy to the Coordinating Center as the scans are read.

F. Other Tasks

1. Participate in the Steering Committee, Imaging Committee, and other subcommittees as needed. Participate in Review Board meetings as needed and assist the Coordinating Center with preparation of Review Board reports.

2. Collaborate with the Steering Committee, Program Office and Coordinating Center to disseminate study findings through publications and presentations at scientific meetings. Provide abstracts and manuscripts proposed for presentation or publication in accordance with NHLBI and CARDIA study policies for approval. As part of the proposal, submit ideas for three manuscripts that would utilize newly collected data and identify specific scientific meetings at which results might be presented.

3. Collaborate with the Coordinating Center to facilitate productive use of CARDIA data and materials by investigators outside the study, with or without direct collaboration of the CARDIA investigators, by providing technical expertise and advice on ultrasound data to outside investigators when requested.

   [Note: In accordance with NHLBI policy on release of data (available at http://www.nhlbi.nih.gov/resources/deca/policy.htm), a limited use data set and documentation will be distributed to outside investigators no later than 5 years after the completion of the closing date of the examination cycle or prior to the termination of the contract, whichever comes first. Data from the follow up component will be distributed no later than 5 years after the last follow up cycle cutoff date.]

4. Provide semi-annual progress reports to the Project Officer. The Reading Center shall report on: administrative matters; current staff (name, position and level of effort); staffing changes; any problems, occurring or anticipated, related to its contract responsibilities and on solutions to the problems; on quality control results; on efforts

to facilitate productive use of CARDIA data and materials by investigators outside the study; and general progress. The Reading Center is expected to review promptly relevant portions of Coordinating Center reports, and to notify the Coordinating Center and the Project Officer of any necessary clarifications or corrections.

5. Provide a final report to the Project Officer, documenting and summarizing the results of the entire contract work, including recommendations and conclusions based on the experience and special results obtained from the Reading Center.

G. Substudies and ancillary studies

Investigators may propose substudies and ancillary studies to be conducted in one or more study Centers. A substudy is an investigation which, although not part of the core exam protocol, will yield information related to CARDIA objectives. An ancillary study is a study that is not funded with CARDIA contract funds. Substudies and ancillary studies may include all or a subgroup of the cohort at a given center, and may involve additional interviews or examinations of study subjects as well as analysis of blood or urine samples, tapes, or images collected previously.

Proposed substudies should: 1) pertain to the main study objectives, 2) produce minimal burden on CARDIA participants, 3) not interfere with other main CARDIA objectives, and 4) require the unique characteristics of the CARDIA cohort.

For each substudy and ancillary study, the principal investigator must provide scientific background and rationale, define the research questions and hypotheses to be investigated and the methodology to be used, state the number and characteristics of participants to be studied providing appropriate rationale, and estimate the burden on CARDIA participants. All substudies and ancillary studies in the proposal should be distinctly identified, with separate descriptions and estimates of costs. Substudies and ancillary studies proposed after the contract award must follow the CARDIA Ancillary Study Policies and be approved by the Steering Committee and the CARDIA Review Board.

Participation in ancillary studies is contingent upon successful efforts in all other aspects of Center functions, particularly those that require resources that overlap with those of the main study.

Exhibit 1 – Project Phasing dated 11/01/2002, 1 page
Exhibit 2 – Travel dated 11/01/2002, 1 page